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Since last year's report we have primarily focused on area II under the technical aims and objectives in the research plan: Reproductive factors and breast cancer risk. Having started the process of working with these questions, we discovered a unique opportunity to differentiate the outcome variable of breast cancer. Previous studies have almost exclusively focused on the influence of different variables describing reproductive history on breast cancer defined as one entity. As it will be described in more detail in the following, we used a large population-based clinical database, including information on tumor size, nodal status, histologic grading, and estrogen receptor status, to address the area of reproductive history and breast cancer risk in an exciting, new way (studies 5,7,8). During this phase, we have also addressed the importance of the gestational age at delivery for subsequent breast cancer risk as an addendum to our earlier abortion study. This has been done by studying preterm delivery and risk of breast cancer (study 6). We have followed the outline of last year's report in the following.

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Papers in press (continued from first year's report)

5. Wohlfahrt J, Mouridsen HT, Andersen PK and Melbye M. Reproductive risk factors for breast cancer by receptor status, histology, laterality and location. Int J Cancer (in press) 1998.

6. Melbye M, Wohlfahrt J, Andersen AMN, Westergaard T and Andersen PK. Preterm delivery and risk of breast cancer. Br J Cancer (in press) 1998.

7. Wohlfahrt J and Melbye M. Maternal risk of breast cancer and birth characteristics of offspring by time since birth. Epidemiology (in press) 1998.

8. Wohlfahrt J, Andersen PK and Melbye M. Multivariate competing risks in a poisson regression model: An application with two correlated characteristics of breast cancer. Stat Med (in press) 1998.

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INTRODUCTION

Study 5: Reproductive risk factors for breast cancer by receptor status, histology, laterality and location

It is well established that a woman's reproductive history influences her risk of breast cancer (Kelsey and Gammon, 1993), but the mechanisms behind are unknown. Hormonal changes induced by a pregnancy could play a role, and because cells in the breast may respond differently to hormone stimuli, the effect of reproductive history on the incidence of breast cancer has been suggested to vary by subtypes of breast cancer.

Until today investigations have pursued this idea by examining whether there are differences in effect of reproductive factors according to oestrogen receptor status. The majority have found nulliparity and late age at first birth only to influence the development of oestrogen receptor positive tumours, but not oestrogen receptor negative tumours (Habel *et al.*, 1993, Stanford *et al.*, 1986, Yoo *et al.*, 1997, Potter *et al.*, 1995).

We extended this line of pursuit investigating in more detail the importance of not only receptor status, but also histology, laterality and location of the tumour using a large population-based cohort of Danish women which was linked to a tumour registry with detailed information on breast tumour characteristics.

Study 6. Preterm delivery and risk of breast cancer

Major hormones influence the development, proliferation, and differentiation of the human breast (Rebar 1994). Based primarily on animal studies, it has been shown that mammary cells proliferate in the first and second trimester of pregnancy and differentiate in the last trimester (Russo et al, 1980). This led Russo and Russo to hypothesize that complete differentiation of the breast cells conveyed by a full-term pregnancy has to be achieved to provide protection against carcinogenic effects. Earlier termination of pregnancy, on the contrary, might increase the risk of breast cancer because proliferation of the breast cells will take place without subsequent differentiation (Russo et al, 1980).

Breast cancer risk in women with a history of a short-term pregnancy has primarily been investigated in relation to spontaneous and induced abortions (Adami et al 1990; Calle et al, 1995; Daling et al, 1994; Kvåle et al, 1987; Michaels et al, 1995; Newcomb et al, 1996; Melbye et al, 1997) which cover the early period of pregnancy. In particular, the large prospective studies have not found such women to be at increased risk of breast cancer (Calle et al, 1995; Kvåle et al, 1987; Melbye et al, 1997). In contrast, few studies have addressed the late period of pregnancy and whether a preterm delivery is associated with an increased risk of breast cancer (Brinton et al, 1983; Rao et al, 1994; Choi et al, 1978; Polednak et al, 1983).

Study 7. Maternal risk of breast cancer and birth characteristics of offspring by time since birth

Hormonal levels during pregnancy may influence the maternal risk of breast cancer. [1] We investigated this hypothesis by studying the association between certain birth characteristics of the latest offspring and the subsequent maternal risk of breast cancer. The birth characteristics showed (birth weight, gender of offspring and multiple births) are related to the hormonal level during pregnancy. [2-8]

Study 8. Multivariate competing risks in a poisson regression model: An application with two correlated characteristics of breast cancer

Studies addressing incidence and risk factors for site-specific cancers often operate with only one ultimate cancer diagnosis. However, a more differentiated outcome, i.e. specific subtypes of the cancer, may often be of interest. In practice, such differentiated analyses can be performed with follow-up data applying Cox or Poisson regression analysis on each subtype separately, but in many situations it is desirable to study whether the risk factors have the same effect on the incidence of different subtypes, the purpose being either to study whether the subtypes have the same aetiology or to obtain a better understanding of the causal pathway behind the risk factors. Such an analysis can be performed as a competing risks analysis testing for identical effects of a risk factor for all or some of the subtypes as discussed for the Cox model by Andersen et al[1] p493ff and for Poisson regression by Pierce and Preston[2].

Sometimes more than one subtype classification is studied. If two such classifications are correlated, one may speculate whether differences in the effect of a risk factor according to one classification simply may be an effect of differences according to the other correlated classification. To evaluate such a hypothesis, we introduce in this paper the new concept of *multivariate competing risks.*

The plan of study 8 is as follows: We will in section two introduce an analysis taken from a breast cancer study as a motivating example for the concept of multivariate competing risks which we, subsequently describe in section three. The method will be illustrated on the example in section four, and finally other applications of the method will be discussed in section five.

BODY

Study 5. Reproductive risk factors for breast cancer by receptor status, histology, laterality and location.

Material and methods

Population Registries
Since April 1, 1968, the Civil Registration System (CRS) in Denmark has assigned an individually unique national registration number to all citizens. This number permits accurate linkage of information from different registries. The Civil Registration System also keeps updated information on dates of live births, emigration and vital status.

In 1977, the Danish Breast Cancer Cooperative Group (DBCG) started a series of national prospective studies to systematically evaluate breast cancer treatment programmes. A detailed description of this registry has been given elsewhere (Andersen and Mouridsen, 1988, Kroman *et al.*, 1997). The DBCG collects detailed information on the breast cancer diagnosis including size, nodal status, receptor status, histology, laterality, location and tumour size. The histological subtypes were categorised according to the WHO classification. The location of a tumour was determined on the basis of an indication, received from the surgical departments, of the location of the tumour on a figure of the four quadrants and the central part of the right and left breasts, respectively. When a tumour was located in the borderline between two areas the tumour was assigned to one of the two (or three) adjacent areas by randomisation.

The presence of oestrogen receptors in the breast cancer tissue was determined by quantitative methods (Thorpe, 1988, Thorpe *et al.*, 1986) or by a semiquantitative method (Andersen *et al.*, 1990). Receptor status was defined by a level of receptor ≥10 fmol/mg cytosol protein for the quantitative assays and/or by staining of ≥10% cells in semiquantitative method. Cases considered oestrogen receptor positive by at least one of the assays are considered as receptor positive.

Through a linkage between the DBCG and the Danish Cancer Registry, the DBCG was found to contain information on 94% of all breast cancer patients reported to the Danish Cancer Registry. The Danish Cancer Registry is considered close to complete regarding incident cases of malignant neoplasms diagnosed in Denmark since 1943 (Storm, 1991)

Study cohort
A research parity database was established from the CRS including all women born between April 1, 1935, and March 31, 1978, as earlier described (Westergaard et al., 1997, Melbye et al. 1997). Based on the person-identifiable CRS number, a linkage was performed with the DBCG giving information on registered invasive primary breast cancers in the period from January 1, 1978, to September 30, 1994.

Statistical analyses
The possible impact of reproductive history on the incidence of different types of breast cancer was investigated in a follow-up study analysed by log-linear Poisson

regression models (Breslow and Day, 1987). All women entered the follow-up for each type of breast cancer on January 1, 1978, or on their 12-year birthday, whichever came last. The period at risk continued until a first time diagnosis of breast cancer (regardless of type), death, emigration, or September 30, 1994, whichever occurred first. Incidence rate ratios are referred to as relative risks. Adjustment was made for age using quadratic splines (with knots: 30,35,40,45,50,55) (Greenland, 1995), calendar period (1978-1982,1983-1988,1989-1992,1993-1994), age at first birth (nulliparous,<20,20-24,25-29,30-34,≥35) and parity (nulliparous, 1,2,3,4+). Splines were used in age adjustment in order to reduce the number of parameters in the type-specific analysis. If there was a relatively small number of cases of a specific subtype, fewer knots were used. All variables were treated as time-dependent. Differences in the asssociation between reproductive history and the incidence fo different subtypes were evaluated by competing risks analysis adjusting for type-specific effects of confounders. P-values for these tests have indices indicating the subtypes compared. For some of the subtypes, the associations with number of births and age at first birth could not be statistically modelled solely by a log-linear trend. All tests and confidence intervals are therefore based on categorised variables. However, in order to describe the overall trends and ease the comparison between subtypes, we have also chosen to give the average risk increase, but without confidence intervals. The average risk increases were estimated with the categorised continuous variables included in the model as continuous variables using the median value within each category as the category score. Traditionally, the risk of breast cancer in nulliparous women is compared with the risk in parous women, disregarding that the parous women have an inhomogenous risk profile according to their reproductive history. To ease the comparison with other studies, we followed this tradition, but in the notes of the tables we compare the risk in nulliparous women with the more homogenous group of parous women with only one birth at the age of 20 to 24 years. All calculations were performed using the SAS procedure PROC GENMOD (SAS Institute Inc, 1996).

Results

In total 1,529,512 women were included in the cohort. Of these, 1,000,276 (65.3%) women had 2,071,415 births before follow-up as follows: 254,694 (25.5 %) had one birth, 494,697 (49.5%) two, 193,250 (19.3%) three, and 57,635 (5.6%) four or more births. A total of 10,790 primary invasive breast cancers were detected in this cohort during 22.3 million person-years of follow-up. Number of cases according to reproductive history, average age at diagnosis, percentage that were oestrogen receptor positive and percentage of tumours that were larger than 2 cm are shown for each type of breast cancer in Table I.

Reproductive history and the risk of breast cancer

Compared with nulliparous women, parous women had a 13% (8%-18%) lower risk of breast cancer. In parous women the risk of breast cancer increased by 10% by each 5-year postponement of the first birth (age(years) at first birth: 12-19: 0.99 (0.93-1.05), 20-24: 1 (ref), 25-29: 1.19 (1.13-1.24), 30-34 1.27 (1.17-1.37), 35+: 1.33 (1.14-1.55)), and there was a 10% decrease in risk by each additional birth: 1 childbirth: 1 (ref), 2 childbirths: 0.97 (0.92-1.02), 3 childbirths: 0.88 (0.82-0.94), 4+ childbirths: 0.70 (0.63-0.77). The association with reproductive history was not significantly modified by age. In women under 45 years of age, parous

women had a significant 10% reduced risk compared with nulliparous, on average an 8% decreased risk per each additional birth, and an 11% increased risk per each 5-year postponement of the first birth. In women over 45 years of age parous women had an 18% reduced risk compared with nulliparous, on average a 12% decreased risk per each additional birth and a 9% increased risk per 5-year postponement of the first birth.

Reproductive history and receptor status
Oestrogen receptor status was available on 6,044 (56%) cases. Of these 68% were oestrogen receptor positive with an average age of 46.5 years at time of diagnosis, whereas patients with oestrogen negative tumours were on average 45.0 years at diagnosis (Table I).

Table II shows the association betwen reproductive history and the incidence of oestrogen receptor negative and positive tumours, respectively. Parous women had a 13% (0%-24%) lower risk of an oestrogen receptor negative tumour compared with nulliparous women and on average a 10% decreased risk by each additional birth. The woman's age at first birth was not significantly associated with her risk of developing oestrogen receptor negative tumours.

Compared with nulliparous women, parous women had a 24%(17%-31%) lower risk of developing a receptor positive tumour. The risk decreased on average by 12% by each additional birth, but was 12% higher by each 5-year increase in age of the woman at her first birth. The association between reproductive history and the incidence of oestrogen receptor positive tumours was not statistically different from the association with the incidence of oestrogen receptor negative tumours, although especially a late age at first birth tended to be stronger related to the risk of receptor positive tumours (12% increase compared with 4%, $p_{ER+ \text{ vs } ER-}=0.07$).

The pattern was the same when restricting to women under 45 years of age and women aged 45 years or more. In women under 45 years of age the risk of estrogen positive and negative tumours decreased by 6% and 5%, respectively, by each additional birth ($p_{ER+ \text{ vs } ER-}=0.81$), but was 17% and 8% higher by each 5-year increase in age of the woman at her first birth ($p_{ER+ \text{ vs } ER-}=0.17$). In women aged 45 years or more the risk of estrogen positive and negative tumors decreased by 11% and 17% by each additional birth ($p_{ER+ \text{ vs } ER-}=0.17$), but was 10% and 2% higher by each 5-year increase in age of the woman at her first birth ($p_{ER+ \text{ vs } ER-}=0.11$).

Reproductive history and histological subtype
Patients diagnosed with ductal carcinomas were on average 44.6 years at diagnosis compared with 46.1 years in patients diagnosed with lobular carcinomas (Table I).

Table III shows the association between parous status, number of births, age at first birth and the incidence of six histological subtypes. As more than 80% of the tumours were ductal carcinomas, the association between reproductive history and the incidence of this subtype was as expected almost identical to the association with the overall incidence of breast cancer. The incidence was 14% lower in parous compared with nulliparous women, the risk decreased on aver-

age by 11% by each additional birth and increased by 9% by each 5-year postponement of the first birth (Table III).

The incidence of lobular carcinomas followed a different pattern (Table III). There was no association with parous status nor number of births. However, by each 5-year postponement of the first birth the risk increased on average by 22%. The association between parous status ($p_{lobular\ vs\ ductal}$=0.10), number of births ($p_{lobular\ vs\ ductal}$=0.09) and the risk of lobular carcinomas was not significantly different from the association with the incidence of ductal carcinomas, but age at first birth was found to have a significantly stronger association with the incidence of lobular carcinomas compared with ductal carcinomas ($p_{lobular\ vs\ ductal}$=0.01).

The risk of developing a mucinous carcinoma was 64%(47%-76%) lower in parous compared with nulliparous women. There was no significant association with number of births but a tendency to an association with a late age at first birth, with a 29% increased risk by each 5-year postponement of first birth (p=0.06). Compared with the associations with the incidence of ductal carcinomas, the association with parous status was significantly stronger ($p_{mucinous\ vs\ ductal}$ <0.001), whereas the association with number of births ($p_{mucinous\ vs\ ductal}$=0.58) and age at first birth ($p_{mucinous\ vs\ ductal}$=0.22) were similar.

The incidence of medullar, papillary and tubular carcinomas was not significantly related to reproductive history (Table III). The lack of association may, however, be due to low statistical power because of the small number of these types. This is further supported by the fact that the associations were statistically similar to the association between reproductive history and the incidence of ductal carcinomas.

Reproductive history and laterality
DBCG registered 10,241 (95%) cases as unilateral breast cancer. (Table I). Of these 5,153 (50.3%) were left-sided and 5,088 (49,7%) were right-sided, i.e. there was a left-right ratio of 1.01 (0.97-1.05). In patients younger than 45 years of age, the left-right ratio was 1.00 (0.96-1.09) and 1.02 (0.96-1.09) in nulliparous and parous women, respectively. Similar figures for patients aged 45 years or older were 1.00 (0.94-1.06), and 1.06 (0.90-1.24). Tumour size, receptor status and age at diagnosis were not related to laterality (Table I).

As shown in table IV, the association between parous status on the incidence of left-sided breast cancer was 0.87 (0.80-0.94) and the association with right-sided breast cancer was 0.88 (0.80-0.96). Similarly, there was the same association between the incidence of left and right-sided tumours by number of births (10% decrease in risk per birth) and age at first birth (12% and 9% increase per 5-year, respectively). This pattern was the same when restricting the analysis to women younger or older than 45 years of age, respectively (data not shown).

Reproductive history on location
Patients with a tumour located non-centrally in the breast were on average 44.6 years old at diagnosis, whereas patients with a tumour located centrally in the breast were 45.4 years old at diagnosis (Table I).

The association between reproductive history and the incidence of breast cancer according to the location in the breast is shown in table V. The incidence of tumours in the four non-central parts of the breast (upper lateral, lower lateral, upper medial, lower medial) was statistically similarly related to reproductive history, and the four non-central sites are therefore considered together in the following. The risk of being diagnosed with a tumour in the non-central part of the breast was 10% lower for parous compared with nulliparous women. On average, the risk decreased by 10% per each additional birth and increased by 9% per 5-year postponement of the first birth (Table V). The incidence of tumours located centrally in the breast was 41% lower in parous compared with nulliparous women. There was no significant association with number births. On average, the risk increased by 30% by each 5-year postponement of the first birth. (Table V). Compared with the associations with non-central tumours, the incidence of central tumours was significantly stronger related to nulliparity ($p_{\text{central vs non-central}}=0.003$) and age at first birth ($p_{\text{central vs non-central}}=0.02$).

Paget's disease in the nipple was registered in 2% of the cases, but in the centrally located tumours the prevalence was 7%. The association between reproductive history and the incidence of centrally located tumours was not altered when excluding cases with Paget's disease in the nipple (67% lower risk in parous compared with nulliparous, 0% risk decrease per additional birth and 30% increased risk per 5-year postponement of the first birth).

Reproductive history and combinations of receptor status, histology and location
Receptor status, histology and location of a tumour are correlated, and the strong associations between a late age at first birth and the incidence of oestrogen receptor positive tumours, lobular and mucinous carcinomas and centrally located tumours may therefore be an expression of the same phenomenon. To investigate this further, we focused on correlated subtypes (e.g. ER+ and lobular carcinoma) and analysed the association between age at first birth and the incidence of combinations of these subtypes.

The percentage of oestrogen receptor positive tumours for each of the described subtypes is shown in Table I. Neither centrally located tumours nor mucinous carcinomas were significantly associated with the oestrogen receptor status, whereas lobular carcinomas compared with ductal carcinomas were more frequently oestrogen receptor positive (85% (465/546) versus 68% (3443/5027), $p<0.001$). We therefore looked at the association between late age at first birth and the incidence of lobular carcinomas according to receptor status. Including only oestrogen receptor negative tumours there was no difference in the association between age at first birth and the incidence of lobular carcinomas (6% increase per 5-year) compared with ductal carcinomas (4% increase per 5-year). In contrast, considering only oestrogen receptor positive tumours, the stronger association with lobular carcinomas (26% per 5-year) compared with ductal carcinomas (10% per 5-year) appeared again. The stronger association between age at first birth and oestrogen receptor positive tumours was seen in both lobular and non-lobular carcinomas.

There was no essential association between neither lobular nor mucinous carcinomas and being diagnosed with a location in the central part of the breast.

We have previously shown late age at first birth to strongly affect especially the incidence of late stage cases as measured by tumour size (Wohlfahrt et al., submitted). As shown in Table I, neither lobular carcinomas nor oestrogen positive tumours were markedly larger at diagnosis compared with ductal carcinomas and oestrogen negative tumours respectively. Tumours located in the central part of the breast, however, were significantly larger at diagnosis compared to non-central tumours (71% (375/525) versus 42% (3822/9052), $p<0.001$). We therefore looked at the association between age at first birth and the incidence of centrally located tumours according to tumour size. In an analysis including only tumours with a tumour size of 2 cm or less, we found the risk of centrally located tumours to increase by 11% per 5-year postponement of the first birth compared to 5% in non-central tumours. Including only tumours with a tumour size of more than 2 cm in the analysis, we found the risk of centrally located tumours to increase by 44% compared with 15% per 5-year in non-central tumours. In other words: the risk increases per 5-year in central compared with non-central tumours are 2.2 (=11%/5%) and 2.9 (=44%/15%) fold higher in analyses in which tumour size was taken into account compared with the 3.3 (=30%/9%) in the overall analysis, as seen in table V. Thus, less than 1/3 of the difference in effect of late age at first birth according to location can be explained by differences in tumour size.

TABLE I - NUMBER OF CASES ACCORDING TO NUMBER OF BIRTHS, AGE AT FIRST BIRTH, AVERAGE AGE AT DIAGNOSIS OF BREAST CANCER, PERCENTAGE OF OESTROGEN RECEPTOR POSITIVE AND PERCENTAGE OF TUMOURS LARGER THAN 2 CM BY SUBTYPE

	Total	Number of childbirths					Age at first birth					Age at diagn.	ER+	tum. size >2cm
		0	1	2	3	4+	12-19	20-24	25-29	30-34	35+	mean(yr)	pct.	pct.
Total	10,790	1,295	1,910	4,892	2,112	581	1,472	4,437	2,693	710	183	44.6	68%	44%
Oestrogen receptor status														
negative	1,910 (18%)	231	330	908	340	101	273	794	456	132	24	45.0	0%	53%
positive	4,134 (38%)	530	732	1,812	840	220	560	1,652	1,038	264	90	46.5	100%	45%
missing[1]	4,746 (44%)	534	848	2,172	932	260	639	1,991	1,191	314	69	42.9	-	39%
Histology														
ductal	8,669 (80%)	1,039	1,528	3,945	1,700	457	1,211	3,561	2,142	564	152	44.6	69%	44%
lobular	963 (9%)	92	160	458	185	68	108	403	276	68	16	46.1	85%	48%
mucinous	143 (1%)	34	27	52	28	2	10	51	35	10	3	44.8	74%	44%
medullary	294 (2%)	27	64	138	49	16	51	116	75	22	3	42.9	20%	50%
papillary	24 (<1%)	1	8	8	6	1	4	11	6	2	0	42.6	63%	47%
tubular	187 (2%)	22	35	82	42	6	28	78	38	19	2	45.6	83%	11%
other	207 (2%)	31	37	90	33	16	28	94	43	8	3	42.6	38%	52%
missing	303 (3%)	49	51	119	69	15	32	123	78	17	4	45.6	64%	43%
Laterality														
left	5,153 (48%)	612	880	2,374	1010	277	735	2,089	1,310	314	93	44.6	68%	44%
right	5,088 (47%)	597	933	2,276	1001	281	661	2,119	1,264	364	83	44.6	69%	44%
bilateral/missing	549 (5%)	86	97	242	101	23	76	229	119	32	7	45.5	69%	47%
Location														
central	586 (5%)	93	99	236	119	39	72	209	153	42	17	45.4	66%	71%
non-central	9,655 (90%)	1,116	1,714	4,414	1,892	519	1,324	3,999	2,421	636	159	44.6	69%	42%
upper lateral	5,643 (52%)	649	1,002	2,579	1,116	297	786	2,335	1,399	375	99	44.6	68%	45%
lower lateral	1,447 (14%)	165	241	679	283	79	187	617	369	88	21	44.8	71%	38%
upper medialt	1,888 (18%)	222	335	844	385	102	267	772	471	124	32	44.5	69%	39%
lower medialt	677 (6%)	80	136	312	108	41	84	275	182	49	7	44.1	65%	36%
bilateral/missing	549 (5%)	86	97	242	101	23	76	229	119	32	7	45.5	69%	47%

1 The relatively low mean age in the missing category is due to the fact that receptor status was not measured routinely in the tthehethearlier mme earlier programmes of DBCG, i.e. the differences disappear when stratifying by calendar period.

TABLE II - ADJUSTED[1] RELATIVE RISK OF BREAST CANCER BY OESTROGEN RECEPTOR STATUS

	ER+	ER−	Test for:
Risk factors	RR (95%-CI)	RR (95%-CI)	ER+ = ER−
Parous[2]			
no	1	1	p=0.09
yes	0.76 (0.69-0.83)	0.87 (0.76-1.00)	
	$p<0.0001$	$p=0.06$	
Number of child-births			
1	1	1	p=0.09
2	0.92 (0.84-1.01)	1.02 (0.89-1.16)	
3	0.89 (0.80-0.99)	0.81 (0.69-0.95)	
4+	0.66 (0.56-0.77)	0.70 (0.55-0.88)	
	$p<0.0001$	$p<0.0001$	
Risk decrease per birth	*12%*	*10%*	
Age at first birth			
12-19	1.01 (0.92-1.12)	1.02 (0.89-1.18)	p=0.07
20-24	1	1	
25-29	1.23 (1.14-1.34)	1.09 (0.97-1.23)	
30-34	1.25 (1.10-1.43)	1.26 (1.04-1.52)	
35+	1.63 (1.31-2.03)	0.93 (0.62-1.41)	
	$p<0.0001$	$p=0.15$	
Risk increase per 5-year	*12%*	*4%*	

[1] Adjusted for type specific effects of age, calendar period, parity and age at first birth

[2] Comparing nulliparous with the more homogenous group of uniparous with a childbirth at age 20-24 the relative risks were: ER+: RR=0.77 (0.68-0.87), ER−: RR=0.89 (0.74-1.06).

TABLE III - ADJUSTED[1] RELATIVE RISK OF BREAST CANCER BY HISTOLOGICAL TYPE

	Ductal	Lobular	Mucinous	Medullary	Papillary	Tubular
Risk factor	RR (95%-CI)	RR (95%-CI)	RR (95%-CI)	RR (95%-CI)	RR (95%-CI)	RR (95%-CI)
Parous[2]						
no	1	1	1	1	1	1
yes	0.86 (0.80-0.91)	1.03 (0.83-1.28)	0.36 (0.24-0.53)	1.32 (0.88-1.97)	2.76 (0.37-20.7)	0.80 (0.51-1.25)
	p<0.0001	*p*=0.80	*p*<0.0001	*p*=0.17	*p*=0.25	p=0.34
Number of childbirths						
1	1	1	1	1	1	1
2	0.97 (0.91-1.03)	1.07 (0.89-1.29)	0.75 (0.46-1.22)	0.84 (0.62-1.15)	0.34 (0.12-0.95)	0.89 (0.59-1.34)
3+	0.82 (0.76-0.88)[3]	0.94 (0.76-1.17)[4]	0.73 (0.42-1.29)	0.63 (0.43-0.92)	0.42 (0.14-1.27)	0.78 (0.48-1.25)
	p<0.0001	*p*=0.26	*p*=0.48	*p*=0.05	*p*=0.13	p=0.57
Risk decrease per birth	*11%*	*3%*	*18%*	*18%*	*34%*	*17%*
Age at first birth						
12-19	1.00 (0.94-1.07)	0.79 (0.64-0.98)	0.57 (0.29-1.13)	1.32 (0.94-1.84)	1.08 (0.34-3.43)	1.05 (0.68-1.62)
20-24	1	1	1	1	1	1
25-29	1.18 (1.11-1.24)	1.38 (1.18-1.61)	1.34 (0.86-2.08)	1.18 (0.88-1.59)	0.99 (0.36-2.73)	0.96 (0.65-1.42)
30+	1.27 (1.14-1.38)[5]	1.39 (1.09-1.78)[6]	1.51 (0.79-2.89)	1.24 (0.79-1.96)	0.81 (0.17-3.95)	1.64 (0.98-2.74)
	p<0.0001	*p*<0.0001	*p*=0.06	*p*=0.36	*p*=0.99	p=0.29
Risk increase per 5-year	*9%*	*22%*	*29%*	*0%*	*-9%*	*6%*

[1] Adjusted for type specific effects of age, calendar period, parity and age at first birth.
[2] Comparing nulliparous with the more homogenous group of uniparous with a childbirth at age 20-24 the relative risks were: Ductal: RR=0.87 (0.79-0.94), Lobular: RR=0.93 (0.70-1.22), Mucinous: RR=0.43 (0.24-0.77), Medullary: RR=1.44 (0.88-2.34), Papillary: RR=5.48 (0.63-47.3), Tubular: RR=0.88 (0.49-1.58).
[3] 3 births: 0.87 (0.81-0.94), 4+ births: 0.67 (0.60-0.74).
[4] 3 births: 0.92 (0.74-1.16), 4+ births: 1.00 (0.74-1.35).
[5] 30-34 years :1.25 (1.14-1.37), 35+ years: 1.36 (1.15-1.61).
[6] 30-34 years: 1.41 (1.08-1.84), 35+ years: 1.31 (0.78-2.19).

TABLE IV - ADJUSTED[1] RELATIVE RISK OF BREAST CANCER BY LATERALITY[2]

	Left	Right	Test for:
Risk factor	RR (95%-CI)	RR (95%-CI)	Left = Right
Parous[3]			
no	1	1	p=0.85
yes	0.87 (0.80-0.94)	0.88 (0.80-0.96)	
	p=0.001	*p*=0.004	
Number of childbirths			
1	1	1	p=0.32
2	1.01 (0.93-1.10)	0.92 (0.85-0.99)	
3	0.90 (0.82-0.99)	0.85 (0.77-0.94)	
4+	0.70 (0.61-0.81)	0.69 (0.60-0.80)	
	p<0.0001	*p*<0.0001	
Risk decrease per birth	*10%*	*10%*	
Age at first birth			
12-19	1.06 (0.97-1.15)	0.93 (0.85-1.01)	p=0.06
20-24	1	1	
25-29	1.23 (1.15-1.32)	1.17 (1.09-1.25)	
30-34	1.20 (1.06-1.36)	1.35 (1.20-1.51)	
35+	1.46 (1.18-1.81)	1.22 (0.97-1.53)	
	p<0.0001	*p*<0.0001	
Risk increase per 5-year	*12%*	*9%*	

[1] Adjusted for type specific effects of age, calendar period, parity and age at first birth.
[2] Bilateral cases are excluded.
[3] Comparing nulliparous with the more homogenous group of uniparous with a childbirth at age 20-24 the relative risks were: Left: RR=0.83 (0.74-0.93), Right: RR=0.92 (0.83-1.03)).

TABLE V - ADJUSTED[1] RELATIVE RISK OF BREAST CANCER BY LOCATION[2]

	Non-central					Central	Test for:
	Upper lateral	Lower lateral	Upper medial	Lower medial	Total[3]	Total	non-centr.
Risk factor	RR (95%-CI)	RR (95%-CI)	RR (95%-CI)	RR (95%-CI)	RR (95%-CI)	RR(95%-CI)	= central
Parous[4]							
no	1	1	1	1	1	1	p=0.003
yes	0.90 (0.83-0.98)	0.90 (0.76-1.06)	0.88 (0.76-1.01)	0.88 (0.70-1.12)	0.90 (0.84-0.96)	0.59 (0.47-0.73)	
	p=0.02	p=0.19	p=0.08	p=0.32	p=0.001	p<0.0001	
Number of childbirhts							
1	1	1	1	1	1	1	p=0.10
2	0.97 (0.90-1.05)	1.03 (0.88-1.20)	0.95 (0.83-1.08)	0.85 (0.69-1.05)	0.96 (0.91-102)	0.98 (0.76-1.25)	
3	0.88 (0.80-0.96)	0.89 (0.74-1.07)	0.90 (0.77-1.06)	0.63 (0.49-0.83)	0.86 (0.81-0.93)	1.07 (0.80-1.43)	
4+	0.67 (0.58-0.76)	0.72 (0.55-0.94)	0.68 (0.54-0.86)	0.71 (0.49-1.03)	0.68 (0.61-0.75)	1.02 (0.69-1.52)	
	p<0.001	p=0.01	p=0.007	p=0.006	p<0.0001	p=0.89	
Risk decrease per birth	*10%*	*9%*	*9%*	*16%*	*10%*	*-2%*	
Age at first birth							
12-19	1.01 (0.93-1.09)	1.01 (0.93-1.09)	1.04 (0.90-1.19)	0.91 (0.71-1.16)	0.99 (0.93-1.06)	0.99 (0.75-1.30)	p=0.02
20-24	1	1	1	1	1	1	
25-29	1.17 (1.09-1.25)	1.17 (1.03-1.34)	1.20 (1.07-1.35)	1.25 (1.03-1.51)	1.18 (1.12-1.24)	1.51 (1.22-1.87)	
30-34	1.27 (1.14-1.42)	1.14 (0.90-1.44)	1.28 (1.05-1.55)	1.31 (0.95-1.79)	1.25 (1.15-1.37)	1.71 (1.21-2.42)	
35+	1.35 (1.10-1.67)	1.11 (0.71-1.74)	1.35 (0.94-1.94)	0.73 (0.34-1.56)	1.27 (1.08-1.49)	2.78 (1.65-4.67)	
	p<0.0001	p=0.053	p=0.01	p=0.04	p<0.001	p<0.0001	
Risk increase per 5-year	*9%*	*9%*	*9%*	*11%*	*9%*	*30%*	

[1] Adjusted for type specific effects of age, calendar period, parity and age at first birth.

[2] Bilateral cases are excluded.

[3] The associations between reproductive history and incidence of the four non-central locations were identical (parous status: p=0.99, number of childbirths: p=0.47, age at first birth: p=0.87).

[4] Comparing nulliparous with the more homogenous group of uniparous with a childbirth at age 20-24 the relative risks were: Non-central: RR=0.91 (0.84-0.99), Central: RR=0.49 (0.35-0.68)).

Discussion

In this study we looked at the association between reproductive history and the incidence of subtypes of breast cancer according to receptor status, histology, laterality and location. The study was performed as a prospective analysis on a large population-based cohort and was based on mandatory reported exposure and outcome information, making information bias on exposure and selection bias on cases unlikely. The estimated effects of reproductive history for each subtype were adjusted for subtype specific age and calendar effects, thus taking into account differential age profiles and secular trends in the diagnosis of the subtypes. The large number of cases furthermore allowed us to study the incidence of combinations of subtypes to evaluate whether differences in the associations between reproductive history and subtype were independent.

Reproductive history and receptor status

In previous studies on reproductive risk factors for subtypes of breast cancer, the main focus has been on oestrogen receptor status. Most studies have found nulliparity and late age at first birth to be risk factors for oestrogen receptor positive tumours only, whereas studies on the effect of additional births have revealed less differences (Habel *et al.*, 1993, Stanford *et al.*, 1986, Yoo *et al.*, 1997, Potter *et al.*, 1995). Our finding is in concordance with this, and in particular, we confirm that a late age at first birth only affects the incidence of oestrogen-positive tumours. The pattern was not modified by age and therefore probably not by menopausal status either.

It has been discussed whether oestrogen status reflects different types of breast cancer or rather different stages in the neoplastic process, with oestrogen-positive tumours gradually becoming oestrogen-negative (Habel *et al.*, 1993). Differences in the association with reproductive history would reflect different risk factors for the various subtypes and, in the latter case, different progression factors between the different stages. Our analysis cannot differentiate between - these to interpretations. However, if oestrogen receptor status reflects different types of breast cancer, our finding of a significant association between the incidence of oestrogen-positive tumours and both nulliparity and a late age at first birth (i.e. high risk of being nulliparous at the initiation of a tumour) would be compatible with the hypothesis that the higher level of oestrogen in nulliparous women can stimulate initiation and promotion of breast tumours.

Reproductive history and histological subtypes

Studies on the association between reproductive history and breast cancer according to histological subtype have been limited and with inconsistent results (Mausner *et al.*, 1969, Morrison, 1976, LiVolsi *et al.*,1982, Rosen *et al.*, 1982, Kvåle *et al.*, 1987, Ewertz and Duffy, 1988, Stalsberg *et al.*,1989, Claus *et al.*, 1993). According to three of these studies (Morrison, 1969, LiVolsi *et al.*, 1982, Stalsberg *et al.* 1989), age at first birth had a stronger effect on (or even restricted to) lobular carcinomas compared with ductal carcinomas, but this is not supported by two other studies (Ewertz and Duffy, 1988, Claus *et al.*, 1993). Our cohort study supported the repeated finding of a significantly stronger effect, but found no evidence of the effect of age at first birth being restricted to lobular carcinomas. Our finding of a stronger association supports the theory according to which additional carcinomas occurring in women with a late age at first birth

originate in the lobules rather than ducts by selectively increasing the number of lobular cells at risk (Stalsberg *et al.*, 1989). But also higher hormonal sensitivity in the cells from which lobular carcinomas originate may play a role, as we observed the strong association to be limited to the oestrogen receptor positive lobular carcinomas.

We found the incidence of mucinous carcinomas in parous women to be 36% (24%-53%) of the incidence in nulliparous women. The association is significantly stronger compared with the association with the incidence of ductal carcinomas, and cannot be explained by differences according to receptor status or tumour size. The finding is in line with Stalsberg et al. (Stalsberg *et al.*, 1989) who observed the incidence of mucinous carcinomas in gravi women to be only 30% of the incidence in nulligravi women ($p<0.01$). We furthermore found a tendency towards a stronger association with age at first birth on the incidence of mucinous carcinomas, which was not reported previously.

It should be noted that the present study only comprises patients in DBCG with available information on reproductive history from the national registries, i.e. women born in 1935 or later. The average age at diagnosis was therefore only 44.6 years. This implies that there is a relatively low proportion of lobular and tubular carcinomas, compared with other settings, as these tumours on average are diagnosed relatively later. For the same reason, there is a relatively higher proportion of medullar carcinomas as they are diagnosed at a relatively early age. However, this introduces no bias as we adjusted for subtype-specific age effects in all analysis.

Reproductive history and laterality
It has become a general belief that the incidence of left-sided breast cancer is higher than that of right-sided breast cancers (Weiss *et al.*, 1996). Two case-studies have found a relation between nulliparity and the left-right ratio. According to the study by Ekbom et al. (Ekbom *et al.*, 1994), nulliparous women under 45 years had a right dominance, whereas Senie et al. (Senie *et al.*, 1980) found left dominance in parous women over 40 years. We found no difference in the association with reproductive history and the incidence of left versus right-sided breast cancer, neither overall nor in women under or over 45 years of age. Therefore, our study does not support the hypothesis that a left-side dominance can be ascribed to reproductive history.

Reproductive history and locality
To our knowledge, no previous reports have focused on the association between reproductive risk factors and the risk of breast cancer according to the localization of the tumour in the breast. In our study, parous status and age at first birth were to a much greater extent related to the incidence of centrally located tumours compared with tumours located non-centrally, and the number of additional births was not associated with the incidence of centrally located tumours. These special associations for centrally located tumors were not related to Paget's disease of the nipple or a special proportion of lobular or receptor positive tumours in this area of the breast.

We have in a previous study shown late age at first birth to strongly affect especially the incidence of late stage cases as measured by tumour size (Wohlfahrt

et al., submitted). Tumours located in the central part of the breast were significantly larger at diagnosis compared with non-central tumours, probably because they may be more difficult to detect. However, we found that less than 1/3 of the difference in the association with age at first birth according to location could be explained by difference in tumour size.

Women diagnosed with a centrally located tumour were on average relatively older compared with women diagnosed with a non-central tumour, and the same pattern was found in patients with lobular compared with ductal carcinomas and oestrogen-positive compared with oestrogen-negative tumours (Table I). For both non-central tumours, lobular carcinomas and oestrogen-positive tumours, we observed a relatively stronger association with age at first birth (and in the first two types no effect of additional births). A common explanation for these findings could be an effect modification by age or menopausal status, with a stronger association with age at first birth and no association with number of births in older women, and in younger women a smaller association with age at first birth and a strong association with number of births. However, if anything, the literature points in the opposite direction (Velentgas *et al.*, 1994), and in our study we found no effect modification by age, but a tendency in concordance with the literature.

Study 6. Preterm delivery and risk of breast cancer.

Material and methods

Registries
We performed a linkage of data from the Danish Civil Registration System (CRS) with the National Birth Registry, the National Hospital Discharge Registry, the National Registry of Induced Abortions, and the Danish Cancer Registry. since April, 1968, the CRS has assigned a unique identification number to all residents in Denmark which permits accurate linkage of information from different registries. The CRS also keeps updated information on dates of livebirths and documents demographic information such as emigration and death.

The National Birth Registry has since 1973 registered all livebirths and stillbirths in Denmark (not including spontaneous and induced abortions). Since 1978, exact (in weeks) gestational age determinations have been included. Gestational age determination is based on information of last menstrual period combined with an early clinical bimanual palpation. In situations of inconsistency between these measures, ultrasound scanning is performed. In the most recent years the use of ultrasound scanning has become widespread and has as such contributed increasingly to the determinations of the gestational age (Sundhedsstyrelsen, 1993). Since 1977, information on spontaneous abortions without specified gestational age has been recorded in the National Hospital Discharge Registry. Information on induced abortions has been recorded in the National Registry of Induced Abortions since reporting became mandatory in 1939. However, information is only available in a computerized format since 1973 (Melbye et al, 1997). The Danish Cancer Registry includes a close to complete registration of cancer diagnoses on all Danish residents back to 1943 (Storm, 1991)).

Subjects
A research database was established from the CRS including all women born in Denmark between April 1, 1935, and March 31, 1978, with information on live-born children. From the National Birth Registry additional information on still-births was added as was gestational age-specific information on all births since 1978. Finally, information on spontaneous (since 1977) and induced abortions (since 1973) was added.

Analyses
The possible impact of gestational age at delivery (stillbirth, preterm, or term delivery) on the risk of breast cancer was investigated among parous women in a log-linear Poisson regression model (Breslow et al, 1987). All women entered the follow-up for breast cancer at the first delivery they had during the period between January 1, 1978, and December 31, 1992, in which gestational age was recorded. Thus, also women with pregnancies before January 1, 1978, were included in the study provided they had a delivery during the study period. The period at risk continued until breast cancer diagnosis, death, emigration, disappearance, or December 31, 1992 (at which time the cancer registration was considered complete), whichever occurred first. Person-years at risk were calculated continuously according to the categorical groups of gestational age of the most recent birth in 1978-92, i.e. women with more than one birth in 1978-92 were in the period between the first and second birth considered at risk according to the gestational age of the first birth; between the second and third birth according to the gestational age of the second birth; and so on. To evaluate the effect of *ever* having a preterm delivery an additional analysis was performed where person-years at risk were calculated continuously in categorical groups according to the birth with the lowest gestational age since 1978.

Adjustments were made for attained age (1-year intervals), calendar period (5-year intervals), age at first birth (12-19,20-24,25-29,30-34,>34 years), and parity (1,2,3,4,5,6,7+ births; including stillbirths, preterm and term deliveries). In an additional analysis we adjusted for history of spontaneous and induced abortion and whether the birth was a stillbirth or a multiple birth. Note that also information on history of spontaneous and induced abortions, stillbirths, and live-births prior to January 1, 1978, was used in the adjustment. Estimation of breast cancer incidence rate ratios was performed using the SAS procedure PROC GENMOD (SAS Institute, 1996). These rate ratios were used as a measure of the relative risk. Test for trend was performed with gestational age treated as a continuous variable and the median gestational age used as the value for each group. The linear assumption in the trend test was checked by a likelihood ratio test against the model with gestational age as categorical variable. Effect modification was evaluated as a test for interaction between categorical variables.

To assess the possible effect of misclassification due to unregistered gestational age in births prior to 1978 we estimated the percentage of person-years of follow up and the number of cases in each cell that might be attributed to the "ever a delivery with a gestational age less than 32 weeks"-category instead of the "never"-category, and then performed the analysis with the adjusted figures. The percentage of person-years was calculated on the basis of the age-specific cumulative incidence at the baseline of the study, and the number of

cases was calculated as the product of the estimated person-years and the rate in the ever category found in the original analysis. The age-specific cumulative incidence of having a delivery with a gestational age less than 32 weeks was calculated using age specific incidence rates seen in 1983 to 1992.

Results

Overall, 474,156 parous women were included in the cohort study. In the follow-up a total of 740,794 births were recorded and distributed as follows: 254,458 women (53.7%) had one birth, 178,700 women (37.7%) had two, 35,791 women (7.5%) had three, and 5,207 women (1.1%) had four or more births. Among these births, 3,261 were stillbirths (0.4%) and 37,347 (5.0%) were preterm (<37 gestational weeks). Preterm births with a gestational age of 32-36 weeks contributed 4.2%, with a gestational age of 29-31 weeks 0.5%, and with a gestational age of less than 29 weeks 0.3 %. The number of women with a preterm delivery was as follows: 32-36 weeks: 29,488 women; 29-31 weeks: 3,702 women; <29 weeks: 2,181 women. Parous women represented a total of 3.8 million person-years of follow-up and 1,363 of these women developed breast cancer. Table 1 presents a detailed distribution of number of breast cancer diagnoses and person-years of follow-up.

As shown in Table 2, we found a significantly increased relative risk of breast cancer in women with a preterm delivery at <29 gestational weeks of 2.11 (95% confidence intervals (CI): 1.00-4.45) and at 29-31 gestational weeks of 2.08 (1.20-3.60), which subsequently dropped as follows: 32-33 weeks: RR=1.12 (0.62-2.04); 34-35 weeks: RR=1.08 (0.71-1.66); 36-37 weeks: RR= 1.04 (0.83-1.32); 38-39 weeks: RR=1.02 (0.89-1.17), 40 weeks: 1 (reference). The continued decline in relative risk observed for preterm deliveries was statistically significant (p-trend=0.04). The trend remained significant after adjustment for history of spontaneous abortion, history of induced abortion, and whether the birth was a stillbirth and/or a multiple birth (p-trend=0.04). A stratified analysis which was performed to evaluate whether the increased risk of breast cancer was associated both with preterm births (liveborn) and preterm stillbirths gave the following result with term deliveries as reference: preterm births with gestational age < 32 weeks: RR=1.98 (1.24-3.16); stillbirths with gestational age < 32 weeks: RR=4.62 (0.42-50.9).

The possible effect modification by age of the woman, number of previous births, age at delivery, and history of previous preterm births or stillbirths is evaluated in Table 3. None of these characteristics significantly modified the risk association observed with gestational age. However, the number of cases in some of the stratified subgroups became very small. We evaluated whether possible temporal changes in the validity and completeness of the ascertainment of the gestational age had a measurable effect on the results by testing whether there was a significant effect modification by period of delivery. This was not the case (p=0.62).

Comparing parous women *ever* having a delivery of less than 32 gestational weeks with other parous women we found a significantly increased risk of 1.72 (1.14-2.59). Considering only parous women ever having a delivery less than 32 weeks gestation, but with the most recent delivery being equal to or longer than 32 weeks gestation, we found no increased risk when comparing to parous

women who never had had a delivery of less than 32 gestational weeks (RR=0.82; 95% CI: 0.26-2.55). However, this result was based on only three cases of breast cancer in this particular group of women.

Based on the age-specific incidence rates of births with a gestational age less than 32 weeks we estimated that less than 2% will ever experience such a delivery. Taking that into account at the baseline of the analysis the rate ratio between parous women ever having a delivery less than 32 gestational weeks and other women increased from 1.72 to 1.73.

Table 1. Distribution of number of breast cancer diagnoses and person-years of follow-up according to reproductive history.

	Preterm delivery				Full-term delivery			
	No. cases	(%)	Person-years ($x10^3$)	(%)	No. cases	(%)	Person-years ($x10^3$)	(%)
Age (years)								
<35	16	(20%)	127	(69%)	315	(25%)	2507	(70%)
35-39	31	(38%)	35	(19%)	417	(32%)	714	(20%)
40-44	24	(30%)	16	(9%)	379	(30%)	299	(8%)
45-49	8	(10%)	5	(3%)	147	(11%)	72	(2%)
50+	2	(2%)	1	(0.4%)	24	(2%)	9	(0.2%)
Age at first birth (years)								
<20	9	(11%)	30	(17%)	93	(7%)	464	(13%)
20-24	24	(30%)	82	(45%	432	(34%)	1728	(48%)
25-29	27	(33%)	52	(28%)	501	(39%)	1107	(31%)
30-34	18	(22%)	15	(8%)	191	(25%)	254	(7%)
35+	3	(4%)	4	(2%)	65	(5%)	48	(1%)
Age at latest birth (years)								
<20	0	(0%)	8	(4%)	1	(0.1%)	105	(3%)
20-24	1	(1%)	47	(26%)	54	(4%)	874	(24%)
25-29	23	(28%)	68	(37%)	351	(28%)	1449	(40%)
30-34	29	(36%)	41	(22%)	513	(40%)	872	(24%)
35+	28	(35%)	20	(11%)	363	(28%)	300	(9%)
Number of previous births								
0	23	(28%)	78	(42%)	240	(19%)	1281	(36%)
1	31	(38%)	68	(37%)	611	(48%)	1609	(45%)
2	19	(24%)	27	(15%)	313	(24%)	553	(15%)
3+	8	(10%)	11	(6%)	118	(9%)	157	(4%)
Previous preterm birth or stillbirth*								
Yes	5	(6%)	12	(7%)	17	(1%)	60	(2%)
No	76	(94%)	171	(93%)	1265	(99%)	3540	(98%)
The delivery was a multiple birth								
Yes	9	(11%)	16	(9%)	20	(2%)	35	(1%)
No	72	(89%)	167	(91%)	1262	(98%)	3566	(99%)

* By *previous* means prior to the most recent pregnancy.

Table 2. Adjusted relative risk of breast cancer in 474,156 parous women according to gestational age at delivery.

Gestational* age (weeks)	No. of cases	Person-years ($x10^3$)	RR (95% CI)
<29	7	9	2.11 (1.00-4.45)
29-31	13	17	2.08 (1.20-3.60)
32-33	11	26	1.12 (0.62-2.04)
34-35	22	58	1.08 (0.71-1.66)
36-37	82	214	1.04 (0.83-1.32)
38-39	350	949	1.02 (0.89-1.17)
40	552	1526	1
>40	326	985	1.03 (0.90-1.18)

* Adjusted for age, calendar period, parity, and age at first birth.

Table 3. Adjusted[*] relative risk of breast cancer in parous women according to gestational age at delivery. Stratified by number of previous births, age, and history of previous pre-term births/stillbirths.

	Gestational age					
	≥ 37 weeks		36-32 weeks		<32 weeks	
	No. cases	RR (ref.)	*No. cases*	RR (95% CI)	*No. cases*	RR (95% CI)
Age of woman[†]						
<40 years	*732*	1	*37*	1.21 (0.87-1.69)	*10*	2.00 (1.07-3.74)
≥ 40 years	*550*	1	*24*	0.88 (0.58-1.32)	*10*	2.11 (1.13-3.95)
Number of previous[‡] births[§]						
0	*240*	1	*17*	1.14 (0.70-1.87)	*6*	2.41 (1.07-5.42)
1+	*1042*	1	*44*	1.03 (0.76-1.39)	*14*	1.94 (1.14-3.29)
Age at delivery[‖]						
<30 years	*406*	1	*20*	1.20 (0.77-1.89)	*4*	1.62 (0.60-4.33)
≥30 years	*876*	1	*41*	1.00 (0.73-1.37)	*16*	2.22 (1.35-3.64)
Previous[‡] pre-term birth[¶] or stillbirth[#]						
No	*1265*	1	*58*	1.06 (0.82-1.38)	*18*	1.97 (1.24-3.14)
Yes	*17*	1	*3*	1.02 (0.30-3.49)	*2*	3.64 (0.84-15.8)

[*] Adjusted for age of the woman, calendar period, parity, and age at first birth., [†] Test for effect modification: p=0.47. A similar lack of effect modification (p=0.73) was found if age of woman was divided by age 50 years., [‡] By *previous* means prior to the most recent pregnancy, [§] Test for effect modification: p=0.86
[‖] Test for effect modification: p=0.67, [¶] Pre-term birth: gestational age < 37 weeks., [#] Test for effect modification: p=0.76

Discussion

Based on this large cohort of almost half a million parous women we found assuring evidence that a preterm delivery of 32+ weeks gestation does not significantly increase the risk of premenopausal breast cancer. Overall, 84% of all preterm deliveries are of 32+ weeks gestation. Only for the small group of preterm deliveries of less than 32 weeks gestation was there a 2-fold increased risk of breast cancer when comparing with a full-term delivery. This elevated relative risk was obtained in an analysis in which a woman's person-years at risk were calculated continuously according to the gestational age of the most recent birth. In an analysis which instead compared parous women *ever* having a delivery of less than 32 gestational weeks with other parous women the risk was 1.7-fold increased. In this last analysis, the preterm birth will not necessarily have been the most recent birth and we speculate whether the somewhat lower estimate could indicate that a full-term birth following a preterm birth might diminish the effect of a preterm birth on breast cancer risk. We found some support for this assumption in a restricted analysis which estimated the risk in parous women ever having a delivery of less than 32 weeks gestation but with the most recent delivery being of 32+ gestational weeks. However, this particular analysis has very limited power.

The analysis of parous women *ever* having a delivery with a gestational age less than 32 weeks compared to other women might be subject to some misclassification, since many of the included women may have had pre-term births prior to 1978. This misclassification, however, is non-differential, and estimating the effect, we found that it was ignorable, as only a very small fraction of women categorised as never having a delivery with a gestational age less than 32 weeks in fact had such a birth prior to 1978.

We used a cohort design for our study based on mandatory reported exposure and outcome information. However, some limitations of the study should be acknowledged. Our gestational age specific relative risk estimates do not follow a smooth curve but instead increase rather abruptly below 32 weeks gestation. This might suggest that the elevated risk of breast cancer among women with a very preterm delivery was a chance finding. However, another explanation would be that the small number of cases with very early preterm deliveries makes it difficult to assess the true magnitude of the effect. In particular, the estimate obtained among women with a preterm delivery of less than 29 weeks was based on only 7 cases of breast cancer and 9,000 person-years of follow-up. However, it is important to note that this estimate did not stand alone but was supported by a similarly increased risk for women with a preterm delivery of 29-31 gestational weeks. We were unable to determine whether the observed risk was due to the preterm delivery per se or the shorter duration of pregnancy. The observation that both women with a preterm stillbirth and women with a preterm livebirth (<32 weeks) had elevated relative risks of breast cancer would be in support of the latter but the figures for stillbirths became very small.

The present study allowed us to consider the influence of potentially confounding factors such as age, age at first birth, parity, multiple births, abortion history, and history of stillbirths. However, several factors (smoking history, body mass index, age at menarche and menopause, family history, oral contraceptives,

postmenopausal hormones) that have been suspected as risk factors for breast cancer could not be accounted for because we lacked the necessary information. The lack of adjustment for such factors would only be important for our results should these factors influence both on the occurrence of breast cancer *and* preterm births. Smoking during pregnancy and high pre-pregnant body weight have been linked to preterm births (Naeye, 1990; Williams et al, 1992). However, there is litle evidence for an association between smoking and breast cancer and the association between body mass and breast cancer remains controversial (Palmer et al, 1993; Hunter et al, 1996). Other factors that have been associated with preterm births are e.g. low social class and low educational level (Pickering et al, 1991). However, breast cancer risk is associated with high social status and thus we would expect the observed relative risks to be underestimated rather than the opposite.

We are not aware of any previous cohort study addressing the risk of breast cancer according to week of gestation at delivery. In a case-control study, Choi et al (Choi et al, 1978) reported an insignificantly 1.4-fold increased risk of breast cancer in premenopausal women who had a terminated pregnancy of more than five gestational months compared to women without such experience. Another case-control study focused on livebirths did not find an increased risk among women with preterm deliveries (Rao et al, 1994) but the total exposure group in that study only counted seven women with a delivery of less than 30 weeks. Stillbirth has not been associated with increased risk of breast cancer, but the available studies have been based on a very limited number of cases and lacked information on gestational length of the pregnancy (Choi et al, 1978; Polednak et al, 1983).

Studies of spontaneous abortion have generally not revealed significantly positive associations (reviewed in Calle et al, 1995). In a recent study by Newcomb et al (Newcomb et al, 1996), a slightly increased risk of breast cancer was recorded but the authors cautioned that the finding might be due to recall bias in their case-control design. Most spontaneous abortions take place early in pregnancy and studies have so far lacked detailed information on gestational week at the time of the abortion. Spontaneous abortion may in certain ways be more like a preterm delivery than an induced abortion but they both represent an interruption of pregnancy (Zang, 1996). The results of case-control studies on induced abortion have been inconsistent with risk estimates ranging from moderately elevated to lowered values (Rosenberg et al, 1994). In a large prospective study we found no overall increased risk of breast cancer after an induced abortion, with the exception of the very small group of women with a late second trimester abortion (Melbye et al, 1997).

In conclusion, a preterm delivery did not significantly increase the woman's risk of contracting premenopausal breast cancer apart from the very small group of women with a preterm delivery of less than 32 weeks gestation. Despite the large size of this study there were only few cases of breast cancer in the subgroups representing the very early deliveries and these results should therefore be considered with due caution.

In the present study we took advantage of the long tradition for mandatory reporting of pregnancy characteristics and cancer diagnoses in Denmark to address in a prospective study whether women with preterm delivery are at increased risk of breast cancer compared to other women.

Study 7. Maternal risk of breast cancer and birth characteristics of offspring by time since birth

Material and methods

Since April 1, 1968, the Civil Registration System (CRS) in Denmark has assigned a unique registration number to all citizens, thereby facilitating accurate linkage of registries. Information on dates and gender of live births, emigration and vital status was obtained from the CRS. From the National Birth Registry we obtained information on dates and gender of stillbirths and information on gestational age (in weeks) and birth weight (in groups of 250 g) on all births since 1973. To identify multiple pregnancies we looked for children (live or stillbirths) born to the same mother within two days.

Invasive primary breast cancers were identified in the Danish Breast Cancer Group's registry (DBCG). [9-10] This registry has since 1978 collected detailed information on the breast cancer diagnosis including the size of the tumor, number of positive nodes, receptor status, histology, localization and laterality. Through a linkage between the DBCG's registry and the Danish Cancer Registry, the DBCG's registry was found to contain information on 94% of all breast cancer patients reported to the Danish Cancer Registry. The Danish Cancer Registry is considered close to complete regarding incident cases of malignant neoplasms diagnosed in Denmark since 1943. [11]

A research parity database was established from the CRS including all women born between April 1, 1935, and March 31, 1978 as earlier described. [12-13] Based on the person-identifiable CRS number a linkage was performed with the DBCG giving information on registered invasive primary breast cancers in the period from January 1, 1978, to September 30, 1994.

We investigated the possible impact of the plurality, birth weight and gender of the latest offspring on the subsequent incidence of the maternal breast cancer risk using a follow-up study, with analysis by log-linear Poisson regression models. [14] All parous women entered the follow-up for breast cancer on January 1, 1978, or on the date of their first childbirth, whichever came last. The period at risk continued until breast cancer, death, emigration, or September 30, 1994, whichever occurred first. Adjustment was made for attained age (≤25,26,27,.....,56,57,58), calendar period (1978-1982,1983-1988,1989-1992,1993-1994), age at first birth (<20,20-24,25-29,30-34,≥35), number of births (1,2,3,4,5,6,7+). As we have previously shown mothers with an extremely preterm birth as the latest birth to have an increased risk of breast cancer[15], we therefore furthermore adjusted for extremely preterm birth (<32 weeks, ≥ 32 weeks, unknown). Due to lower number of cases in the tumor size-specific analysis number of births were categorized (1,2,3,4+) and age adjustment was performed by quadratic splines (with knots: 30,35,40,45,50,55). [16] All variables were treated as time-dependent variables. Using year of birth instead of calendar period had no effect on the results in Tables 1 and 2. No residual confounding was revealed by adjustment with a main effect of time since latest birth categorized more than "<5 years" and "≥5 years". The numbers of person-years at risk for birth characteristic groups were calculated according to birth characteristics of the latest birth, as the focus was the effect in the first years after delivery. Women with more than one birth were, in the period between the first and the second birth, considered at risk according to the characteristics of the first birth; between the second and the third birth they were considered at risk according to the

characteristics of the second birth; and so on. In the analysis of gender and birth weight of offspring, the observation periods with the latest birth as a multiple birth were excluded from follow-up.

Results

During the 12.8 million person-years of follow-up 9,495 cases of breast cancer aged 22 to 58 years were identified.

In table 1 the association is shown between birth characteristics of a woman's latest birth and her risk of breast cancer according to the time interval since the birth. In the first 5 years following a multiple versus a singleton birth, the risk of breast cancer was higher (RR=1.8 (1.1-2.8)). The higher risk was seen in both uniparous (RR=1.9 (0.8-4.6) and multiparous (RR=1.7 (1.0-3.0) mothers. After 5 years there was no appreciably increased risk (RR=1.1 (0.9-1.3)). Mothers delivering a heavy-weighted child subsequently had a higher risk of breast cancer compared with mothers delivering a small child. The risk increased by 10% per 1 kilogram increase in birth weight (RR_{trend}=1.1 (1.0-1.2) per kg) (Table 1). In the first 5 years following a birth the risk of breast cancer increased by 20% per kg (RR_{trend}=1.2 (1.0-1.5) per kg). The trends were RR_{trend}=1.1 (0.8-1.5) per kg and RR_{trend}=1.2 (1.0-1.5) per kg in uniparous and multiparous, respectively. After the 5-year period the relative increase per kg was 10% (RR_{trend} =1.1 (1.0-1.2) per kg). According to additional analysis, mothers delivering a child with a birth weight from 3.75 up to 4 kg and larger than 4 kg, respectively, both had a 10 % overall higher risk ($RR_{3.75kg-4kg}$ =1.1 (1.0-1.2), $RR_{>4kg}$ =1.1 (1.0-1.3)) compared with mothers with a newborn of 3 kg or less. There was no difference in the breast cancer incidence according to gender of the child (Table 1).

Additional information on the characteristics of the breast cancer at diagnosis and the large number of cases in each birth weight category allowed us to estimate the risk according to birth weight of latest offspring by tumor size (Table 2). The overall increase in risk during the first 5 years following a birth in mothers delivering a heavy-weighted child was primarily due to an increase in larger tumors (>2 cm) (RR_{trend}= 1.5 (1.1-2.1) per kg). The effect on small tumors (≤2 cm) was smaller (RR_{trend}=1.2 (0.8-1.6) per kg). The effect of birth weight of offspring in the first 5 years after the birth was seen primarily on the incidence on estrogen negative (RR_{trend} =1.3 (0.8-2.1) per kg) compared with estrogen positive tumors (RR_{trend} =0.9 (0.6-1.3) per kg).

TABLE 1. Adjusted* effect of birth characteristics of latest offspring on the maternal risk of breast cancer overall and according to time since latest birth.

Birth characteristics of the latest offspring	Person years	Rate Ratio overall		Rate Ratio according to time since latest birth <5 years		≥5 years	
		no.	RR(95%-CI)	no.	RR (95%-CI)	no.	RR (95%-CI)
Multiple birth							
no	$12{,}592 \times 10^3$	9,327	1	663	1	8,664	1
yes	185×10^3	168	1.1 (1.0-1.3)	18	1.8 (1.1-2.8)	150	1.1 (0.9-1.3)
Birth weight[†,‡]							
≤ 3 kg	$1{,}617 \times 10^3$	739	1	115	1	624	1
3-3.25 kg	$1{,}241 \times 10^3$	560	1.0 (0.9-1.1)	78	0.9 (0.7-1.2)	482	1.0 (0.9-1.1)
3.25-3.5 kg	$1{,}610 \times 10^3$	758	1.0 (0.9-1.1)	130	1.1 (0.9-1.5)	628	1.0 (0.9-1.1)
3.5-3.75 kg	$1{,}388 \times 10^3$	666	1.0 (0.9-1.1)	116	1.1 (0.9-1.4)	550	1.0 (0.9-1.1)
>3.75 kg	$2{,}063 \times 10^3$	1151	1.1 (1.0-1.2)	198	1.2 (0.9-1.5)	953	1.1 (1.0-1.2)
Increase in risk per kg[§]			1.1 (1.0-1.2)		1.2 (1.0-1.5)		1.1 (1.0-1.2)
Gender[†]							
boy	$6{,}422 \times 10^3$	4,786	1	331	1	4,455	1
girl	$6{,}170 \times 10^3$	4,541	1.0 (1.0-1.0)	332	1.0 (0.9-1.2)	4,209	1.0 (0.9-1.0)

*Adjustment was made for attained age, calendar period, age at first birth, number of births and extremely preterm birth.
[†] Only singleton births are included.
[‡]Only mothers with a birth from 1973 and onwards are considered in these analyses.
[§]Birth weight was treated as a continuous variable, with the median for each category as the category value.

TABLE 2. Adjusted* effects of birth weight of latest offspring on the maternal risk of breast cancer according to time since latest birth and tumor size at diagnosis.

Birth weight of the latest offspring	Rate ratio according to time since latest birth and tumor size at diagnosis							
	< 5 years				≥ 5 years			
	≤2 cm		>2 cm		≤2 cm		>2 cm	
	no.	RR (95%-CI)	no.	RR (95%-CI)	no.	RR (95%-CI)	no.	RR (95%-CI)
Birth weight†								
≤ 3 kg	51	1	46	1	346	1	240	1
3-3.25 kg	40	1.1 (0.7-1.6)	27	0.8 (0.5-1.3)	261	1.0 (0.8-1.2)	194	1.1 (0.9-1.3)
3.25-3.5 kg	61	1.2 (0.8-1.8)	55	1.2 (0.8-1.8)	328	0.9 (0.8-1.1)	252	1.0 (0.9-1.2)
3.5-3.75 kg	49	1.1 (0.7-1.6)	52	1.2 (0.8-1.8)	280	0.9 (0.8-1.1)	236	1.1 (0.9-1.3)
>3.75 kg	91	1.2 (0.9-1.7)	93	1.4 (0.9-1.9)	495	1.0 (0.9-1.2)	409	1.2 (1.0-1.4)
Increase in risk per kg‡		1.2 (0.8-1.6)		1.5 (1.1-2.1)		1.0 (0.9-1.2)		1.2 (1.0-1.4)

*Adjustment was made for attained age, calendar period, age at first birth, number of births and extremely preterm birth.
†Only singleton births are considered and only mothers with a birth from 1973 and onwards are included in these analyses.
‡Birth weight was treated as a continuous variable, with the median for each category as the category value.

Discussion

The present study was motivated by the hypothesis that hormone-associated birth characteristics of offspring are related to the maternal risk of breast cancer in the first years following a birth. Our population-based cohort study supported this hypothesis, as we found an increased risk of breast cancer in mothers with multiple births or heavy-weighted newborn children in the first 5 years following the birth, whereas the associations diminished in subsequent years. Due to our prospective study design it is unlikely that these results are subject to selection bias or differential misclassification.

Mothers with a multiple birth or a heavy-weighted newborn child are likely to have higher estrogen concentrations (oestradiol, oestriol and unconjugated oestriol) during pregnancy. [2-4] The increased risk in these mothers during the first five years after birth is therefore compatible with the idea that estrogen is involved in the etiology of breast cancer, and the increased incidence of large tumors in mothers with a heavy-weighted newborn child furthermore supports the idea that also the progression of occult tumors may be affected. We note that the effect on breast cancer risk of a multiple birth is larger compared with a delivery of a relatively heavy child. This finding could be due to a larger difference in hormonal levels in mothers having a multiple versus singleton birth compared with a heavy-weighted versus light-weighted child.

Women with diabetes may have an increased risk of breast cancer[17,18] and their offspring have a higher average birth weight due to the higher concentrations of different growth factors in these women. Part of the increased risk in mothers with heavy-weighted newborn children could therefore also be attributed to a high proportion of diabetics among these mothers.

A few studies of mothers with multiple births have previously reported an increased risk of breast cancer in the first years following a multiple birth. [19-21] However, these studies have compared the incidence to all other mothers irrespective of the time factor, meaning time since latest birth. Thus previously published effects cannot be separated from the overall short-term increased risk of breast cancer after a birth reported by Lambe and Albrektsen. [22-23] By analyzing the short-term effect of birth characteristics as an effect modification of the overall effect of time since latest birth, we avoided this problem, and found that indeed there is a higher short-term risk in mothers with a multiple birth or a heavy-weighted newborn child compared with others.

Women with high body mass index (BMI) have an increased risk of breast cancer. [24] Mothers that deliver a heavy-weighted child on average have a higher BMI themselves, which may explain the overall enhanced risk in these mothers. Furthermore, part of the increased incidence of large tumors might be due to difficulties for early detection in these women because of more breast tissue. However, it cannot explain why the effect is largest in the first 5 years following a birth. Furthermore, most studies indicate that the negative effect of high BMI is restricted to post-menopausal women, whereas in this study most women are in a pre-menopausal age group in the first five years following a birth.

In conclusion, we found support for the hypothesis that hormone-associated birth characteristics influence the maternal risk of breast cancer in the first five years following a birth. This is compatible with the idea that hormonal changes during pregnancy influence the subsequent short-term risk of breast cancer.

Study 8. Multivariate competing risks in a poisson regression model: An application with two correlated characteristics of breast cancer

Material and methods

2. A MOTIVATING EXAMPLE

The concept of multivariate competing risks was developed in the course of analysing a follow-up study of breast cancer. The study was based on information on breast cancer cases from the Danish Breast Cancer Cooperative Group[3] and a population-based cohort of Danish women with information on vital status and reproductive factors[4,5]. In the cohort of 1.5 mill women (22.3 mill person-years) we identified 10,790 women with breast cancer.

The purpose of the following analysis was to investigate whether a woman's number of (live)births, besides being an important risk factor for breast cancer as such[6], was predictive for the severity of the disease at diagnosis, in order to select women for a targeted breast cancer screening. The analysis was performed as a competing risks analysis comparing the effect of number of births on the incidence of breast cancer according to two measures of severity at diagnosis: tumour size (≤20mm, 21-50 mm, >50 mm) and number of positive nodes (no positive nodes, 1-3 positive nodes, and 4 or more positive nodes).

Both tumour size and nodal status reflect different stages rather than different subtypes. A competing risks analysis might therefore not seem to be the obvious approach because a breast cancer with a tumour size larger than 50 mm at diagnosis must have been 10 mm previously, i.e. the 'types' do not seem to compete. However, competing risks models are applicable in this setting because the two classifications are measures of severity *at diagnosis* and a case can only have a single level of severity at diagnosis according to a given classification scheme. Nevertheless such an approach does not allow for differentiation between differences in progression and detection rate, i.e. an aetiologically more relevant explanation of why differences may exist. The following analysis is, therefore, primarily meant as an illustration on the use of multivariate competing risks rather than a definitive aetiological analysis of the data at hand.

The competing risks analysis (described in detail in section 4.1) revealed that number of births had a stronger effect on the incidence of small tumours compared to the effect on the incidence of larger tumours. Similarly, the effect on the incidence of node-negative breast cancers was stronger than the effect on the incidence of node-positive cases. As small tumours tend to be node-negative it is natural to speculate whether the two findings reflect the same phenomenon. An intuitive way to evaluate this hypothesis is to look at the effect of number of births on the incidence of different combinations of tumour size and nodal status, and then see whether the relatively stronger effect on the incidence of small tumours can be found in both node-negative and node-positive cases. The concept of multivariate competing risks analysis formalises this intuitive idea, and we will now describe the method in detail.

3. MULTIVARIATE COMPETING RISKS MODELS

3.1 Multivariate competing risks models using Cox regression

If the purpose of a study is to evaluate the effect of an exposure on the rates of a specific type of outcome (e.g. breast cancer), the rate for individual i is commonly modelled in a log-additive model as $l_i(t) = l_0(t)\exp(bx_i)$, with t representing age and x_i being a coded variable representing the exposure for women i. Extension to several exposures and adjustment for confounders is well known. To ease notation, the index i will be dropped in the following.

If instead of only one type there are J subtypes of outcome, one can apply a competing risks model, with the cause specific rates modelled as: $l_j(t) = l_{0j}(t)\exp(b_j x)$, with t being age and $j=1,...,J$ outcome subtype. In this model the effect of the exposure is different for each subtype outcome, and the likelihood function factorizes corresponding to j completely separate models. The model with the same effect of the exposure for all outcome subtypes can be stated as $l_j(t) = l_{0j}(t)\exp(bx)$. In this model the likelihood function does no longer correspond to j completely separate models, however, the model can still be analysed using standard Cox regression techniques as described in Andersen et al[1] p. 493ff.

In order to introduce the multivariate competing risks model we will now describe the situation where two subtype classifications ($j=1,...,J$ and $k=1,...,K$) of outcome are being studied simultaneously. As a straightforward extension of the previous model one can consider the cross-product of the two subtype classifications letting $l_{jk}(t)$ be the rate of having subtypes j and k simultaneously and t representing age. These rates could be modelled as $l_{jk}(t) = l_{0jk}(t)\exp(b_{jk}x)$, i.e. a model with different baseline hazards and different effects of exposure for all combinations of subtypes. This would be a standard competing risks model. However, a more parsimonious log-additive model would be $l_{jk}(t) = l_{0jk}(t)\exp(b^0x + b^1{}_jx + b^2{}_kx)$, where the effect of the exposure is log-additive on both subtype classifications. This model offers a natural means for testing for no differences in effects according to one subtype classification when adjusting for differences according to the other subtype classification, i.e. testing the models: $l_{jk}(t) = l_{0jk}(t)\exp(b^0x + b^1{}_jx)$ or $l_{jk}(t) = l_{0jk}(t)\exp(b^0x + b^2{}_kx)$. These models for $l_{jk}(t)$ are what we will propose to call *multivariate competing risks models* as they can be applied for analysing two or more sets of competing risks, making it possible to test hypotheses about the multivariate effect of risk factors on these sets of competing risks. The models can be analysed using the same techniques as for standard 'univariate' competing risks models, with cause specific rates for every combination of subtypes.

3.2 Multivariate competing risks models using Poisson regression

Under the assumption of piecewise constant baseline rates the Cox regression model is identical to a Poisson regression model. Poisson regression often provides a more feasible approach in large studies since one may work with abbreviated tables of cases and person-years at risk rather than with the individual data records[7].

Competing risks analysis using Poisson regression can be performed if an extra dimension in the cross-classification of cases according to the type of disease is created as described for linear models by Pierce and Preston[2] and for log-linear models by Larson[8]. Person-years at risk are independent of this factor. Test for the same effect of a risk factor is then simply a test for no interaction between the risk factor and this new factor.

Multivariate competing risks models can be analysed using Poisson regression following the same arguments and techniques as for 'univaritate' competing risks models, i.e. by creating an extra dimension according to each of the $J \cdot K$ combinations of subtypes. However, in order to facilitate the new parsimonious additive models this extra dimension should be further classified into two new dimensions according to each of the two classifications (i.e., with J and K levels, respectively). Tests for hypotheses of identical effects of the risk factor according to classification number one can be performed as a test for no interaction between the risk factor and the factor according to classification number one while including an interaction term between classification number two and the risk factor.

4. THE EXAMPLE REVISITED

We will now return to the example introduced in section 2. We will shortly describe the 'univariate' competing risks analyses and thereafter illustrate multivariate competing risks models.

4.1 The 'univariate' competing risks analysis

Due to the large number of observations the breast cancer rates were analysed using log-linear Poisson regression models, i.e. assuming piecewise constant baseline rates. The effects of number of births according to number of positive nodes were estimated in three independent models of the form:

$$l_j(t) = l_{0j}(t) \exp[a_{period,j} + b_{age\ 1.\ birth,j} + d_{no.\ of\ births,j}],$$

with j being the number of positive nodes (0,1-3,4+) and $a_{period,j}$, $b_{age\ 1.\ birth,j}$ and $d_{no.\ of\ births,j}$ being the node-specific effects according to levels of calendar period, age at first birth and number of births. A significant effect of number of births was found for breast cancers with no positive nodes (p<0.0001) or one, two or three positive nodes (p=0.0006), whereas there was no effect of number of births on the risk of breast cancer cases with four or more positive nodes (p=0.42) (Table 1). Whether these differences in effect could be due to chance can be answered within the framework of competing risks, i.e. by testing whether $d_{no.\ of\ births,j} = d_{no.\ of\ births}$. Doing so, we found a significant difference between the effects of number of births on the incidence of breast cancer according to the number of positive nodes, i.e. a significant interaction between number of births and the dummy variable created according to the number of positive nodes in the breast cancer cases
(Likelihood ratio test: -2log$Q$=33.07, d.f.=6, p<0.0001) (Table 1).

Similarly, a significant effect of number of births was found for breast cancers with size ≤20 mm (p<0.0001) or 21-50 mm (p=0.012), whereas there was no effect of number of births on the incidence of large tumours (p=0.98) (Table 1). As for number of positive nodes, the three effects of number of births were significantly different although the differences were less pronounced (Likelihood ratio test: -2log$Q$=13.41, d.f.=6, p=0.04).

4.2 The multivariate competing risks analysis

Number of positive nodes and tumour size are highly correlated and it is therefore natural to speculate whether the latter finding simply reflects differences according to number of nodes. The effects of number of births for each combination of tumour size and number of positive nodes are presented in Table 2. The differences in the effect of number of births according to number of positive nodes that were significant in the 'univariate' competing risks analysis remained

significant within constant levels of tumour size (≤20 mm: p=0.02, 21-50 mm: p=0.02, >50 mm: p=0.38). However, the data disclosed a tendency to a uniform effect of number of births according to tumour size within a constant level of number of positive nodes (0 nodes: p=0.11, 1-3 nodes: p=0.95, 4+ nodes: p=0.62). Application of a multivariate competing risks model makes it possible to make a formal test of whether there is a uniform effect of number of births according to tumour size adjusted for differences according to number of positive nodes.

In this multivariate competing risks model we initially checked whether the differences in effects in Table 2 could be described as a log-additive effect of differences according to tumour size and differences according to number of nodes, i.e. a test of

$$l_{jk}(t) = l_{0jk}(t)\exp[a^1_{period,j} + a^2_{period,k} + b^1_{age\ 1.\ birth,j} + b^2_{age\ 1.birth,\ k} + d^1_{no.\ of\ births,j} + d^2_{no.\ of\ births,k}]$$

against

$$l_{jk}(t) = l_{0jk}(t)\exp[a^1_{period,j} + a^2_{period,k} + b^1_{age\ 1.\ birth,j} + b^2_{age\ 1.\ birth,k} + d_{no.\ of\ births,jk}]$$

with j being number of positive nodes and k the tumour size. This was accepted (Likelihood ratio test: -2log$Q$=15.11, d.f.=12, p=0.24). The underlying assumptions of log-additivity for the effects of calendar period and age at first birth were checked using the same types of test (data not shown).

Finally, we tested whether there were differences in the effect of number of births according to tumour size or number of positive nodes, i.e. the hypothesis $d^1_{no.\ of\ births,j} = d^1_{no.\ of\ births}$ and $d^2_{no.\ of\ births,k} = d^2_{no.\ of\ births}$. The estimates based on this multivariate competing risks model clearly demonstrated that the differences according to tumour size can be ascribed to differences according to number of nodes (Likelihood ratio test:
-2log$Q$=2.29, d.f.=6, p=0.89). While there were no differences relative to the reference effect for tumour size, there were still noticeable differences for number of positive nodes when adjusting for tumour size (Likelihood ratio test: -2log$Q$=22.37 d.f.=6, p=0.001).

Table 1 The adjusted effect of number of births on the breast cancer incidence according to number of positive nodes and tumour size.

Breast cancer characteristics	Number of births				Likelihood ratio test for effect (d.f.=3)	Likelihood ratio test for interaction (d.f.=6)
	1 child (ref.)	2 children RR (95%-CI)	3 children RR (95%-CI)	4 or more children RR (95%-CI)		
Positive nodes*						
0 nodes	1	0.97 (0.90-1.05)	0.82 (0.75-0.90)	0.59 (0.51-0.68)	$p<0.0001$	$p<0.0001$
1-3 nodes	1	0.98 (0.88-1.09)	0.89 (0.79-1.01)	0.71 (0.59-0.85)	$p=0.0006$	-2logQ=33.07
4+ nodes	1	0.98 (0.85-1.13)	1.08 (0.91-1.28)	1.11 (0.89-1.39)	$p=0.42$	
Tumour size‡						
≤20mm	1	0.95 (0.89-1.03)	0.83 (0.76-0.91)	0.61 (0.53-0.70)	$p<0.0001$	$p=0.04$
21-50 mm	1	0.98 (0.89-1.08)	0.90 (0.80-1.01)	0.80 (0.68-0.94)	$p=0.012$	-2logQ=13.41
>50 mm	1	1.00 (0.80-1.25)	0.99 (0.76-1.29)	1.06 (0.74-1.52)	$p=0.98$	

*Adjustment made for node-specific effects of age, calendar period and age at first birth.
‡Adjustment made for size-specific effects of age, calendar period and age at first birth.

Table 2 The adjusted* effect of number of births on the breast cancer incidence according to combinations of number of positive nodes and tumour size.

Number of nodes	Number of births	Tumour size ≤20 mm RR (95%-CI)	Tumour size 21-50mm RR (95%-CI)	Tumour size >50mm RR (95%-CI)	Likelihood ratio test for interaction (d.f=6)
0 positive nodes	1 child	1	1	1	p=0.11
	2 child.	0.95 (0.86-1.04)	1.00 (0.87-1.16)	0.74 (0.43-1.27)	-2log$Q$=10.28
	3 child.	0.78 (0.69-0.87)	0.86 (0.72-1.02)	1.08 (0.60-1.95)	
	4+ child.	0.56 (0.47-0.67)	0.61 (0.47-0.79)	1.30 (0.62-2.75)	
1-3 positive nodes	1 child	1	1	1	p=0.95
	2 child.	0.97 (0.83-1.12)	0.97 (0.82-1.15)	0.99 (0.65-1.50)	-2log$Q$=1.60
	3 child.	0.87 (0.73-1.04)	0.87 (0.71-1.06)	0.78 (0.47-1.31)	
	4+ child.	0.65 (0.50-0.85)	0.80 (0.60-1.06)	0.55 (0.24-1.26)	
4+ positive nodes	1 child	1	1	1	p=0.62
	2 child.	0.99 (0.74-1.33)	0.91 (0.74-1.10)	1.07 (0.79-1.45)	-2log$Q$=4.42
	3 child.	1.24 (0.90-1.71)	0.98 (0.78-1.23)	1.04 (0.73-1.49)	
	4+ child.	0.98 (0.62-1.55)	1.11 (0.82-1.51)	1.10 (0.68-1.78)	
Likelihood ratio test for interaction (d.f.=6)		p=0.02 -2log$Q$=14.98	p=0.02 -2log$Q$=14.95	p=0.38 -2log$Q$=6.41	

*Adjustment made for size and node-specific effects of calendar period and age at first birth and for the effect of age for each of the nine combinations of size and nodal status.

Discussion

We have with the above example illustrated the use of the concept of multivariate competing risks introduced in section 3. Using a competing risks model we showed that a woman's number of births is predictive of the severity at diagnosis of breast cancer, measured as tumour size or nodal status. We speculated whether these two findings reflected one phenomenon, and with the use of the multivariate competing risks analysis we were able to formally confirm this hypothesis.

As noted, the example chosen for illustrative purposes does not evaluate an aetiological hypothesis as one cannot distinguish between differences in progression and detection rates. An example of a multivariate competing risks analysis of a aetiological hypothesis within breast cancer research would be to compare risk factors for receptor negative versus receptor positive breast tumours. Many have found that reproductive risk factors might be stronger for oestrogen receptor positive than for oestrogen receptor negative tumours and some have found the same relation using the progesterone receptor status[9]. Progesterone receptor status and oestrogen receptor status are highly correlated. It has, therefore, been speculated, whether these two results reflect the same phenomenon[9]. Multivariate competing risks models offer a natural way to analyse this hypothesis with follow-up data.

Furthermore, it has been speculated that certain combinations of the oestrogen and progesterone receptor status might be more related to reproductive history than others[10]. This opens for yet another use of the multivariate competing risks model, because this can be studied as a goodness-of-fit test for the additive model. We have performed these analyses in our dataset, however, the multivariate competing risks analyses turned out less useful in this case as we found no strong relation between progesterone receptor status and reproductive history in the 'univariate' competing risks analysis.

In the models described above we have used a multiplicative modelling of competing risks. However, it could be argued that competing risks are intrinsically additive, and that the effects of the two classifications should not be mutually multiplicatively adjusted. An alternative model could, therefore, be to adjust them additively in a more complicated model like

$$\lambda_{jk}(t) = \lambda_{0jk}(t)\exp[a^1_{period,j}+a^2_{period,k}+b^1_{age\ 1.\ birth,j}+b^2_{age\ 1.birth,k}] \cdot(\exp(d^1_{no.\ of\ births,j}) +\exp(d^2_{no.\ of\ births,k}))$$

This will no longer be a standard log-linear model of the rates but it could be analysed as a Poisson regression model using Epicure[11].

In conclusion, we have here introduced a new type of competing risks models which we think, may prove relevant in practical situations.

CONCLUSIONS

Based on the studies undertaken so far, the following conclusions were reached regarding topics covered under category II:

II. Reproductive history and breast cancer

Study 5:
Overall, the incidence in parous women increased by 10% by each 5-year postponement of their first birth. For the incidence of lobular carcinomas this increase was significantly stronger and for mucinous carcinomas it tended to be stronger than for ductal carcinomas. For the incidence of centrally located tumours the increase was stronger than for non-centrally located tumours. On average, there was a 10% decrease in breast cancer risk by each additional birth. This decrease was seen in most subtypes, but not for lobular carcinomas and centrally localised tumours. According to our findings, lobular and mucinous carcinomas and centrally located tumours may have risk factor profiles which differ from other types of breast cancer.

Study 6:
A preterm delivery did not significantly increase a woman's risk of contracting pre-menopausal breast cancer apart from a very small group of women with a preterm delivery of less than 32 weeks' gestation. Despite the large size of the this study, there were only few cases of breast cancer in the subgroups representing the very early deliveries, and these results should therefore be considered with due caution.

Study 7:
Mothers having a multiple birth compared to singleton mothers had an increased risk of breast cancer in the first five years after a birth (RR=1.8; (95% CI 1.1-2.8). Mothers having a heavy-weighted child compared with a lighter-weighted child were also at increased risk (RR_{trend}= 1.2 (1.0-1.5) per kg). This latter effect was primarily due to an increased incidence of tumors larger than 2 cm at diagnosis (RR_{trend} =1.5 (1.1-2.1) per kg). Our findings are compatible with the hypothesis that the hormonal level during pregnancy influences the risk of breast cancer in the early years after delivery.

Study 8:
Competing risks models can be used to compare the effect of risk factors for different causes of death or subtypes of a disease. However, sometimes more than one outcome classification is available and if two such classifications are correlated, one may speculate whether differences in the effect of a risk factor according to one classification simply may be an effect of differences according to the other correlated classification. We introduce in this paper the new concept of *multivariate competing risks* to formally test such a hypothesis.

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